Remarks

Claims 1-20, 29-45, and 54-69 were pending in this application. Applicants thank the Examiner for considering Applicants' response to a restriction requirement filed on May 18, 2004. Claims 1-20, 29-45, and 54-57 are withdrawn from consideration because they allegedly read on a non-elected invention. Claims 58-69 remain pending and have been rejected. Applicants amend claims 58, 60, 63, 68 and 69 to specifically recite reducing inflammation in a subject, and add new claims 70 and 71. Support for this amendment and new claims can be found, for example, at least at page 1, lines 20-24; page 21, line 34 to page 22, line 17; page 23, lines 24-26; page 26, lines 7-9; and page 27, lines 17-22.

Applicants respectfully request consideration and examination of this application and the timely allowance of the pending claims 58-71 in view of the arguments below.

Formalities

Applicants thank the Examiner for bringing to the Applicants' attention certain sequences in the application which were missing SEQ ID NOs. Accordingly, Applicants have amended the specification to introduce SEQ ID NOs:43 to 48. Additionally, Applicants submit a substitute Sequence Listing in accordance with 37 C.F.R. §§1.821-1.825 and a computer readable form of the substitute Sequence Listing. No new matter is added.

Applicants also thank the Examiner for pointing out certain trademarks that appear in the application. Applicants have capitalized such trademarks where they appear.

Enablement Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 58-69 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification as-filed. Applicants note that the Examiner acknowledges that the specification teaches that PSGL peptides comprising region 42-60 can bind to P-selectin and interfere with the binding of P-selectin with PSGL-1. (8/10/04 Office Action at page 4). The Examiner, however, alleges that there is no guidance, *in vitro* or *in vivo*, to indicate that this interaction is sufficient to inhibit leukocyte/endothelial cell interaction, which would be required to inhibit inflammation. *Id.*

The Examiner points out that the claims are not drawn to inhibition of inflammation but to treatment of diseases. The Examiner continues by arguing that even if the claimed invention inhibits inflammation, it may not be sufficient to treat multi-component diseases where inflammation is only one component of the disease. *Id.*

The Examiner further relies on *Ulbrich* et al. (Trends in Pharmacology, pp 640-647 (2003)) ("*Ulbrich*") to allege that because *Ulbrich* teaches that a fusion protein of PSGL-1 failed in clinical trials, it would be undue experimentation for a skilled artisan to practice the claimed invention. *Id.* Specifically, it appears that because of a discussion in *Ulbrich* that certain agents that affected selectin binding did not have a therapeutic effect on myocardial infarction, the Examiner is concerned that it would require undue experimentation for one skilled in the art to use the fusion proteins of the claimed invention for the various claimed therapeutic uses.

Applicants have amended the claims to describe the claimed subject matter in clearer terms. Accordingly, the amended claims are now drawn to methods of reducing inflammation using compositions of the invention. Applicants respectfully submit that the amended claims are fully enabled by the specification as filed, in view of the arguments below.

Applicants note that the test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosure in the patent application coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 U.S.P.Q.2d 1217, 1222 (Fed. Cir. 1988). The law allows some reasonable experimentation, however, does not require Applicants to disclose each and every embodiment of the claimed invention.

Applicants submit that one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation in view of the disclosure of the instant specification coupled with information that was known in the art at the time of filing. For example, the specification discusses that it was well known in the art that during inflammation, leukocytes/platelets adhere to vascular endothelium via binding of P-selectin to its ligands. *See*, for example, page 1, lines 20-34.

The claimed invention provides compositions which have inhibitory activity for selectin-mediated intercellular adhesion, thereby acting as anti-inflammatory agents. *See*, for example, page 27, lines 17-22. For example, the specification discusses that by blocking binding of PSGL to P-selectin, the adherence of leukocytes to sites of inappropriate inflammation is either abolished or markedly reduced. *See*, for example, page 26, lines 3-5. Applicants note that the Examiner has acknowledged that the

specification is enabling for PSGL-1 fusion proteins comprising 42-60 amino acids which can bind to P-selectin and interfere with its binding to PSGL-1. *Id.* The Examiner, however, alleges that it is not clear whether such compositions would inhibit interaction between leukocytes and endothelial cells, as would be required for inhibiting inflammation.

Applicants submit that the specification provides assays for measuring interaction between cells expressing P-selectin and those expressing PSGL-1. *See*, for example, Examples 4 and 6, which provide assays for measuring interaction between COS cells expressing PSGL and CHO cells expressing P-selectin. Applicants understand that while the specification does not specifically use leukocytes and endothelial cells in such interaction assays, compounds identified as blocking interaction between cells expressing P-selectin and those expressing PSGL-1, can be used for blocking interaction between any two cells where such interaction is mediated via P-selectin and PSGL-1.

For example, Applicants submit a reference (Theoret et al. J. Pharm. Expt. Therapeutics, Vol. 298 (2): 658-664 (2001) ("*Theoret*")) which evidences that a soluble form of PSGL-1 can inhibit the interaction between leukocytes/platelets and endothelial cells, as one skilled in the art would have predicted based on the instant specification. Applicants enclose a courtesy copy of this reference for Examiner's convenience. *Theoret* discusses that a recombinant soluble form of PSGL protein inhibited binding of platelets with neutrophils on endothelial cells, which is mediated via P-selectin and PSGL. *See* Abstract. Additionally, page 663 of *Theoret* discusses that it would be beneficial to block interaction of P-selectin with PSGL in many inflammatory and

thrombotic reactions using a recombinant soluble form of PSGL, also as discussed in the instant specification. Accordingly, Applicants submit that *Theoret* just confirms what the instant specification teaches, that interaction of cells expressing P-selectin and PSGL-1, such as leukocytes and endothelial cells, can be blocked with a soluble form of PSGL-1, and that blocking such interaction would be beneficial in treatment of many inflammatory and thrombotic disorders, some of which are recited in the instant claims.

Additionally, Applicants submit that *Ulbrich*, which is cited as allegedly rendering the claimed invention non-enabling, is misleading and irrelevant. The instant claims, as amended, are directed to methods of reducing inflammation using a PSGL fusion protein which comprises amino acids 42 to 60 of SEQ ID NO:2 and a non-PSGL amino acid sequence. *Ulbrich* fails to specifically discuss this specific PSGL fusion protein. *Ulbrich* discusses that blocking selectin activity has been attempted in several clinical disorders. *See* page 642, right hand column. *Ulbrich* further discusses that certain drug candidates failed in clinical trials to protect against inflammation induced by ischemic conditions. *See* page 644, left hand column. Applicants note that the only fusion protein comprising PSGL discussed in *Ulbrich* is rPSGL-Ig, which was reported to have no therapeutic effect for treatment of myocardial infarction. *See* page 642, Table 1.

Applicants note that none of the pending claims are specifically drawn to the treatment of myocardial infarction. Accordingly, Applicants note that the observation that rPSGL-Ig including amino aids 42 to 88 of SEQ ID NO:2 was not effective for treating myocardial infarction, is irrelevant to reducing inflammation in a subject, either independent, or which occurs in association with another condition. Accordingly,

Applicants submit that an observation that rPSGL-Ig was not effective in treating myocardial infarction has no bearing on the instant claims.

It is not clear from *Ulbrich*, however, whether this rPSGL-Ig contains amino acids 42 to 60 of SEQ ID NO:2, as required by the instant claims. *Ulbrich* cites to another reference, Diaz-Ricart et al., Drugs of the Future, 27(4): 346-349 (2002), ("*Diaz-Ricart*"), which provides further details regarding the fusion protein discussed in *Ulbrich*. (*See* Diaz-Ricart et al., Drugs of the Future, 27(4): 346-349 (2002)). Applicants enclose a courtesy copy of that reference for Examiner's convenience.

Applicants note that the rPSGL-Ig fusion protein of *Ulbrich*, which is discussed in *Diaz-Ricart*, is a PSGL protein which comprises 47 amino acids from the N-terminal end of the extracellular domain of mature PSGL-1 fused at the hinge region of human IgG. Applicants understand that this form corresponds to a fusion protein including amino acids 42 to 88 of PSGL-1. *Diaz-Ricart* discusses that while the development of recombinant PSGL including amino acids 42 to 88 of SEQ ID NO:2 was discontinued for treatment of myocardial infarction due to disappointing results in clinical trials, it does not rule out the use of this molecule for treatment of other indications. *See*, column 2, page 348.

Further, Applicants submit references evidencing that a soluble form of PSGL protein, rPSGL-Ig protein including the first 47 amino acids from the N-terminus fused to human IgG1 was effective in reducing inflammation in various conditions. For example, the Abstract of Wang *et al.*, Journal of American College of Cardiology, Vol. 38(2): 577-582 (2001) ("*Wang*"), discusses that P-selectin antagonism using rPSGL-Ig decreased neointimal hyperplasia following balloon injury by inhibiting inflammatory and thrombotic

responses at the site of balloon injury. Also, Gasser *et al.*, Journal of American Society of Nephrology, Vol. 13: 1937-1945 (2002) ("*Gasser*") discusses that treatment with rPSGL-Ig prevented the early inflammatory changes in the transplanted organs. *See*, Abstract. Applicants enclose copies of these references for Examiner's convenience. Accordingly, *Wang* and *Gasser* demonstrate that the claimed compositions are capable of reducing inflammation in a subject, as one of ordinary skill in the art would have predicted based on the instant specification coupled with the information known in the art at the time of filing.

Additionally, Applicants submit yet another reference, Battistini *et al.*, Blood, 101(12): 4775-4782 (2003) ("*Battistini*"), which discusses the role of PSGL-1 in an important inflammatory response in multiple sclerosis, which we note is one of the diseases recited in the instant claims. In particular, *Battistini* discusses the importance of PSGL-1 in the recruitment of particular type of lymphocytes, i.e., $CD8^+$ T cells, in early inflammation in multiple sclerosis. *See*, for example, the Abstract, which discusses that blocking PSGL-1 using antibodies resulted in blocking recruitment of $CD8^+$ T cells in brain vessels of patients with multiple sclerosis. *Battistini* discusses that $CD8^+$ T cells from patients with multiple sclerosis have a higher capacity to adhere to P-selectin, which is expressed by acute and subacute inflamed endothelium. *See*, column one, page 4780. *Battistini* is able to block recruitment of $CD8^+$ T cells which express PSGL-1 to endothelium expressing P-selectin in multiple sclerosis patients, by using antibodies to PSGL-1, thereby reducing inflammation. Accordingly, *Battistini* only further supports Applicants' claimed invention which uses a soluble form of PSGL-1, instead of an antibody, to reduce inflammation in a subject with an inflammatory disease

such as multiple sclerosis, by blocking adhesion of cells expressing PSGL-1, e.g., $CD8^+$ T cells and endothelium.

In view of the foregoing, Applicants submit that the instant claims are fully enabled by the specification as-filed and respectfully request that this rejection be reconsidered and withdrawn.

CONCLUSION

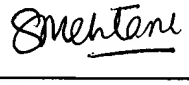
In view of the foregoing remarks, Applicants respectfully request withdrawal of this rejection and timely allowance of the pending claims. Should the Examiner have remaining questions or concerns regarding this application, Applicants request that the Examiner contact the undersigned at 617-452-1606 to schedule an interview to discuss the application.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 7, 2005

By: 

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